REMARKS

Claims 1-25 are pending. Claims 9-11 stand withdrawn from consideration. Claims 26-28 have been added. Claims 1-8 and 12-28 will therefore be pending upon entry of the proposed amendments.

Applicants have amended claim 1 to further clarify that the claimed kits require "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a reconstitution solution of mixed solvents." Support for this amendment can be found throughout the Specification, e.g., at page 2, line 21 through page 3, line 7. Applicants have also replaced the phrase "including water-soluble material" in claim 1 with "comprising water-soluble material" as suggested by the Examiner.

Applicants have replaced the phrase "the didemnin is chosen from" in claim 3 with "the didemnin compound is selected from the group consisting of" as suggested by the Examiner.

Applicants have replaced the phrase "including a water-soluble bulking agent" in claim 8 with "comprising a water-soluble bulking agent" as suggested by the Examiner.

Applicants have amended claim 21 to depend from claim 20 instead of claim 12.

Support for new claims 26-28 can be found throughout the Specification, e.g., at page 2, line 21 through page 3, line 14.

No new matter is introduced by these amendments.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-8 and 12-25 are rejected on various grounds for allegedly being indefinite. Each of the grounds for rejection is addressed individually below.

Claim 1 is rejected because the phrase "a lyophilized didemnin preparation including water-soluble material and a reconstitution solution of mixed solvents" is allegedly "unclear" (Office Action, page 2). According to the Office, "[t]he above phrase seems to be inconsistent to what is claimed in claim 8 and claim 20 whereas the lyophilized didemnin preparation appears to be separate from the reconstitution solution" (Office Action, page 2).

Applicants have replaced the phrase "a lyophilized didemnin preparation including water-soluble material and a reconstitution solution of mixed solvents" in claim 1 with "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a reconstitution solution of mixed solvents." In other words, the claimed kits require the separate presence of the lyophilized didemnin preparation and the reconstitution solution, e.g., the presence of two containers or enclosures: one holding the lyophilized didemnin preparation and its associated water-soluble material, and the other holding the reconstitution solution of mixed solvents.

Applicants respectfully request reconsideration and withdrawal of the rejection in view of the amendment to claim 1 and the foregoing remarks.

Claim 3 is rejected because "the phrase the didemnin is chosen ... should be more consistent with with claim 15" (Office Action, page 2). This rejection is moot in view of the amendment to claim 3.

Claim 8 is rejected because of the use of the transitional phrase "including" in claim 8 (Office Action, page 3). This rejection is moot in view of the amendment to claim 8.

Claims 21 and 22 are rejected because there is "insufficient antecedent basis" for the limitation "the alkanol/water mix" (Office Action, page 3). According to the Office, "there is insufficient antecedent basis for the limitation in the claim because the limitation is not recited in Claim 1" (Office Action, page 3).

Applicants respectfully disagree. Claim 21 as currently amended and claim 22 depend directly and indirectly, respectively, from claim 20 and not from claim 1. Claim 20 recites the limitation "an alkanol/water mix" in the body of clause (i). Applicants submit that base claim 20 therefore provides sufficient antecedent basis for the recitation of "the alkanol/water mix" in claims 21 and 22.

Applicants respectfully request reconsideration and withdrawal of the rejection in view of the amendment to claim 21 and the foregoing remarks.

Rejection under 35 U.S.C. § 102

Claims 1-4 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Crumb et al., U.S. Patent 6,030,943 (Crumb). According to the Office:

> Crumb et al. anticipate the claimed invention (i.e. column 5 lines 50-67 and column 6 lines 1-21, see especially lines 16-21 of column 6) because Crumb et al. teach a pharmaceutical composition may be in the form of a container (i.e., the kit is a container) comprising firstly of a lyophilized didemnin preparation comprised of a didemnin (i.e. aplidine) and a water soluble material (i.e. mannitol) and secondly a reconstitution solution comprised of carriers such as mixed solvents (i.e. water and surfactants) (Office Action, page 4).

Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

The present claims are directed to kits and pharmaceutical compositions that are applicable for the parenteral administration of didemnin compounds (e.g., aplidine). Claims 1-8 as currently amended are directed to kits that include "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a reconstitution solution of mixed solvents."

Crumb does not disclose a kit or any other article of manufacture that includes a first container or enclosure containing a lyophilized didemnin preparation comprising water-soluble material and a second container or enclosure containing a reconstitution solution of mixed solvents. Rather, Crumb discloses articles in which mixtures of aplidine and pharmaceutically acceptable carriers are enclosed **together** within a **one** container and **not** separately within **two** containers as required by the present claims. In addition, while Crumb discloses lyophilized aplidine preparations, these preparations are expressly disclosed as being used in conjuction with reconstitution media that contain a single solvent, namely sterile water, and not mixed solvents as required by the present claims. These points are discussed in more detail below.

The Office relies upon the following passages in Crumb as the basis for the rejection: col. 5, lines 50-67 and col 6, lines 1-21. Both of these passages are reproduced below and are labeled "A" and "B," respectively (emphases added):

A. Such pharmaceutical compositions comprise at least Aplidine as the active ingredient and a pharmaceutically acceptable carrier. In making such pharmaceutical compositions, **the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper or other container**. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material, which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, ...

B. ...starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

For oral administration, Aplidine can be admixed with carriers and diluents molded into tablets or enclosed in gelatin capsules. The mixtures can alternatively be dissolved in liquids such as ten percent aqueous glucose solution, isotonic saline, sterile water, or the like, and administered intravenously or by injection. **Such solutions can, if desired, be lyophilized and stored in a sterile ampoule ready for reconstitution by the addition of sterile water for ready intramuscular injection**.

With regard to A, Crumb discloses that aplidine (and not a lyophilized preparation of aplidine) can be "enclosed within" a single carrier, such as a "capsule, sachet, paper or other container" (Crumb, col. 5, line 55). There is no mention of a reconstitution solution of any kind, let alone a reconstitution solution of mixed solvents. Moreover, there is no mention of a second container, much less a second, separate container containing a reconstitution solution of mixed solvents. The Office has asserted that "the kit is a container" (Office Action, page 4). In view of

the foregoing, even in the case where the containers disclosed in Crumb should be a kit, such a kit would contain a **single** container of aplidine and a carrier, but not a second container having a reconstitution solvent as required by the present claims. Further, even if a kit is a "container," it is a single container and does not suggest the separate or two-container or enclosure configuration of the present claims.

Applicants now turn to passage B, which makes the first and only mention of a lyophilized aplidine preparation. Crumb expressly discloses that such lyophilized preparations are reconstituted using only reconstitution media that contain a **single** solvent, namely sterile water, and not mixed solvents as required by the present claims (Crumb, col. 6, lines 17-20, emphasis added):

> Such solutions can, if desired, be lyophilized and stored in a sterile ampoule ready for reconstitution by the addition of **sterile water** for ready intramuscular injection.

There is no teaching or suggestion in Crumb to use reconstitution media other than sterile water. In this regard, Applicants note that a surfactant is not a solvent. Thus, contrary to the assertion of the Office, a water/surfactant mixture is not a mixed solvent.

Applicants submit that Crumb does not disclose a kit or any other article of manufacture that meets all of the limitations of claims 1-4 and 6 as currently amended. As such, claims 1-4 and 6 are not anticipated by Crumb. Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-8 and 12-25 are rejected as being unpatentable over Crumb in view of Gyory et al., U.S. Patent 5,883,135 (Gyory). According to the Office (Office Action, page 6):

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Crumb et al.'s pharmaceutical composition and/or kit to include Gyory et al.' alkanol active ingredient within Crumb's pharmaceutical composition and/or kit because the two combined teachings would create an improved claimed pharmaceutical composition and/or kit for enhance delivery of the pharmaceutical composition's active ingredients to a subject.

Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

As mentioned elsewhere, the present claims are directed to kits and pharmaceutical compositions that are applicable for the parenteral administration of didemnin compounds (e.g., aplidine). Claims 1-8 as currently amended are directed to kits that include "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a reconstitution solution of mixed solvents." The kits provide a stable dosage form that can be reconstituted for administration by injection. Claims 12-25 are directed to reconstituted pharmaceutical compositions that include: a didemnin compound; a water soluble material; a surfactant; an alkanol; and water.

Crumb's parenteral formulations are exclusively single solvent-based, not mixed solvent-based formulations (Crumb, col. 6, lines 14-20):

> The mixtures can alternatively be dissolved in liquids such as ten percent aqueous glucose solution, isotonic saline, sterile water, or the like, and administered intravenously or by injection. **Such solutions can, if desired, be lyophilized and stored in a sterile ampoule ready for reconstitution by the addition of sterile water for ready intramuscular injection**.

Crumb's formulations include as the liquid component either sterile water or aqueous solutions that further contain non-solvent components, such as salt (e.g., saline) or glucose. There is no teaching or suggestion in Crumb to use delivery or reconstitution media other than water-based media, much less mixed solvent delivery or reconstitution media that include alkanols and water.

Crumb teaches the use of water as a reconstitution solution for rehydrating a lyophilized didemnin preparation. Gyory teaches a solution of drug (not a didemnin, didemnins are not mentioned in Gyory) with water and alcohol as an electrotransport composition that enhances the flux of a drug through a body surface such as skin. In particular, Gyory reports at col. 3, lines 49-55 that the composition reduces electrical resistance of body surfaces. That has nothing to do with Crumb. It likewise has nothing to do with the problem addressed by the present inventors (see, e.g., pages 2-3 of the present Specification), namely reconstitution of a lyophilized preparation, e.g., to provide a stable dosage form that can be reconstituted for administration by injection. Gyory's attempts to solve the problem of dermal permeability has nothing to do with the use in Crumb. It also has nothing to do with the claimed invention, which is the reconstitution of a lyophilized didemnin. There is no teaching in Gyory that the water or alcohol or mixture of the two should or could be used to reconstitute a lyophilized preparation of any drug, let alone didemnin. The use of alkanol to facilitate electrotransport through the skin has nothing to do with reconstituting a lyophilized preparation or providing a kit suited for providing a reconstituted solution, e.g., for parenteral administration. They are completely unrelated.

One reference, Crumb, is at best, about reconstitution of a lyophilized solution. The other, Gyory, is about dermal electrotransport. There is no teaching in Gyory to start with a lyophilized preparation and no teaching that the mixed solvent would be useful or work to reconstitute a lyophilized preparation, let alone a lyophilized preparation of didemnin. Gyory simply teaches that its solution, i.e., drug, water, and alcohol, is useful in a transdermal device for movement of the drug into the skin. So, Crumb teaches one solvent (water) for the purpose of rehydrating a lyophilized preparation. Gyory teaches a different solution (alcohol and water) for a different use, i.e., a liquid to contain a drug in a transdermal device. There is no mention of rehydrating a lyophilized preparation in Gyory.

Thus, there is no motivation to select two components (i.e., alcohol and water) of the dermal electrotransport drug solution in Gyory and substitute them for the reconstitution solution of Gyory (i.e., water) for a different purpose, reconstitution, in Crumb. Further, and perhaps even more importantly, there is no reasonable expectation the alcohol/water solution of Gyory would work to rehydrate didemnin. Crumb explicitly tells one to use water. There is no reasonable expectation that something that works in a transdermal delivery device would work as a reconstitution solution. Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants submit that all claims are in condition for allowance.

Enclosed is a $120 check for the One Month Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 14620-012US1.

Respectfully submitted,

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